sub-sarcolemmal caveolae and caveolar structure with pressure load, and conduction slowing was attenuated. Cardiomyocyte caveolar localization and conformation change with increased ventricular load, and this alteration appears to play an important role in load-induced conduction slowing, possibly by contributing to changes in effective membrane capacitance.

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Ionic Mechanism for the Formation of Excitable Scroll Wave Filaments

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Scroll waves revolving at high frequency in the heart are responsible for fatal arrhythmias. Some mechanisms of arrhythmias require scroll waves to revolve at high frequency around an excitable filament. Recent ventricular cell models including calcium dynamics cannot reproduce this phenomenon. We address this problem revising sodium current kinetics and key phase II inward currents. We perform a nonlinear analysis of the sodium current gathered in canine cardiac myocytes. Despite an extensive data set, our nonlinear analysis shows that several Hodgkin-Huxley formalisms, i.e., a model family, reproduce the voltage clamp data. We incorporate formalisms taken from this family in the latest version of the Luo and Rudy cell model (LRd) and explore the parameter space for scroll wave dynamics. The simulations are performed on a monolayer of cells (3cm x 3cm) and portions (about 2/3) of the left ventricular free wall with realistic representation of the microanatomy. The Bidomain equations are solved at a resolution of 100um in space and 100us in time and are carried out on a supercomputer of the Texas Advanced Computer Center.

Our bifurcation analysis shows that sodium current formalisms associated with higher threshold and slightly slower rate of rise during early depolarization may be more realistic. When combined with relatively minor revision of phase II plateau inward currents, the LRd model can produce scroll waves revolving around an excitable filament. The revised model exhibits a rotation period significantly briefer than the original one, and even briefer than the refractory period measured on a plane wave. This mode of excitation allows us to study mechanisms of cardiac death.

In conclusion, revision of sodium current kinetics and phase II inward currents of the LRd model allows to realistically reproduce scroll wave revolving around unexcited filament.

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Computational Predictions of Tissue-Specific Consequences of Long QT Mutations: Role of the Purkinje Fiber

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The long QT syndrome (LQTS) is a heritable cardiac disorder that leads to prolongation of ventricular repolarization, episodes of ventricular arrhythmia, and sudden cardiac death. Mounting evidence has implicated the Purkinje fiber (PF) conduction system in the genesis of ventricular arrhythmias. This study assesses for tissue-specific consequences of the biophysical alterations induced by LQTS-related mutations, using computational models of ventricular and PF cells. Mutations causing LQT1 and LQT2 (in KCNQ1 and HERG, respectively) are first simulated by reducing density of the respective components of the delayed rectifier current. These mutations prolong action potential duration (APD) in ventricular myocytes more than in their PF counterparts, due to differences in the conductance and activation of plateau potassium currents between the two cell types. Next, the canonical LQT3 mutation delKPQ (in the cardiac NaV 1.5 sodium channel, encoded by SCN5A) is modeled in both tissue types (as described previously, by increasing entry into a bursting mode of channel gating, producing substantial late non-inactivating inward current). Marked APD prolongation is confirmed in both tissue types, exacerbated by slow stimulation rates or pauses in pacing. Simulation of another SCN5A mutation, F1473C, which clinically produces severe QT prolongation and heavy arrhythmia burden, is shown to have a markedly larger effect on PF cells than ventricular myocytes (including a propensity for repetitive early afterdepolarizations), owing to a depolarizing shift in the mutant channel availability and lower plateau potential in PF. Finally, the interactions between PF and ventricular cells at the tissue level are investigated in the context of these mutations in a cable model representing a section of ventricular wall. In conclusion, the biophysical alterations induced by LQT mutations may have significant tissue-specific consequences, with important implications for arrhythmia and its therapy.

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Optical Screening of Electrical, Mechanical, and Signaling Function on Adult Cardiac Myocytes as Alternative QT-Screen

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QT interval prolongation is a biomarker for ventricular tachyarrhythmias and a risk factor for sudden death. It is well known that some drugs can prolong the QT interval. QT-interval screens are recommended by FDA for nearly all new molecular entities. Preclinical QT screens include animal experiments and patch-clamp based methods solely screening for alterations in heterologously expressed hERG channel conductance in cell lines. The aim of the present study was to explore the recording conditions and define settings which allow the optical screening of multiple electrophysiological parameters in isolated cardiac ventricular myocytes as an alternative to traditional QT-screens. Here we has show that modern calcium and voltage fluorescent probes allow for high temporal resolution (under 3 ms) of cytoplasmic calcium and membrane potential transients in beating adult cardiac myocytes. A novel approach allowing for simultaneous measurements of intracellular calcium and cell contractions using fast line scanning mode of laser confocal microscope is described. Concomitant ratiometric detection of voltage sensitive probes fluorescence allowing for motion artifacts correction is also discussed.

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Impact of Multiple Ionic Changes in Arrhythmic Risk Biomarkers in Human Ventricular Electrophysiology

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Electrophysiological variability represents an important challenge in evaluating cardiac response to disease and drug action. Our goal is to quantitatively evaluate the sensitivity of biomarkers to the simultaneous alteration of several ionic current in human cardiomyocytes. Computer simulations of human ventricular electrophysiology are conducted using an action potential (AP) model proposed by Carro et al.

Ionic current conductances and kinetics were simultaneously varied by +/-30%. Model output was evaluated by quantifying biomarkers including AP duration (APD) and triangulation. Statistical techniques based on experiments design along with a second order response surface model were used.

Results reveal that simultaneous alteration of several ionic properties results in nonlinear effects in biomarkers response. APD is more sensitive than triangulation to changes in ionic properties. 30% changes in sodium/potassium pump and in calcium inactivation result in APD values outside the physiological range (287-350ms; Fig. 1A).

In contrast, 30% changes in most ionic properties result in triangulation within physiological range (70-86ms). However, simultaneous reduction of GKr and GCaL by 30% significantly increases triangulation (Fig. 1B).

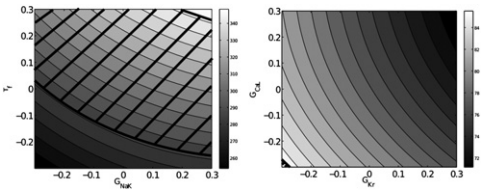

Figure 1. A) AP duration, B) AP triangulation. Marked area indicates physiological range

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Action Potential Duration Maps in Homogeneous Cardiac Ventricular Tissue Slices are Independent of Changes in Stimulation Site

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Cardiac slices are an increasingly popular model system for cardiac electrophysiology research, as they combine ease of handling with patho-physiologically relevant cell-type representation and distribution. The revival of the cardiac slice technique, first established in the 1980's[1] has been linked to improved techniques for preparation and monitoring. It now offers a well-posed target for computational modelling of cardiac structure-function interrelations.

This study used slices from the New Zealand white rabbits (female, ~1kg, n=12), cut tangentially to the left ventricular wall surface (350um thick, ~1x2cm large), offering a simplified 'pseudo-2D' experimental model. Slices, loaded with Di-4-ANBDQPQ (voltage sensitive dye; 10uM) to optically monitor action potential duration (APD), were stimulated at four different sites with concentric-bipolar point-electrodes, using a biphasic rectangular pulse 50% above activation threshold and, for comparison, with field stimulation.

APD at 50% and 80% repolarization (APD50 and APD80, respectively), was used to establish APD-maps in each slice. Locally-resolved average APD patterns were obtained for pacing frequencies of 1-4Hz. In addition, at each slice location the